EXHIBIT B

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Customer No.: 07278
PATENT TRADEMARK OFFICE

Docket No: 3671/0J107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Armin Prasch et al.

Serial No.: 09/845,682 Art Unit: 16450

Confirmation No.: 2295

Filed: April 26, 2001 Examiner: Jean C. Witz

For: Fibrin tissue adhesive formulation and process for its preparation

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DECLARATION UNDER RULE 132

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

PETER C. SCHMIDT, declares as follows:

1. I am a Professor at the Pharmaceutical Institute, Tübingen University, located at Auf der Morgenstelle 8, D-72076 Tübingen, Germany.

2. I have read the information set forth in U.S. Patent Application No. 09/845,682 ('682

Application) and WO 97/44015 ('44015 Application).

3. I have been asked by Applicants, through their representative, Pfenning, Meinig & Partner, to explain the differences between U.S. Patent Application No. 09/845,682 and WO application 97/44015 in a comparative assessment.

4. The '682 Application and the '44015 Application both make use of fibrinogen and thrombin as active ingredients for a fibrin adhesive formulation, with calcium chloride, albumin, sugar or sugar substitutes as other ingredients.

5. According to the '44015 Application, the ingredients are dissolved in water and then subjected to spray drying at an inlet temperature of 100 °C and an outlet temperature of 65 °C using a Schlick nozzle of type 970/0 with an atomizing pressure of 1 bar. In the '44015 application, thrombin and fibrinogen are processed separately because processing together in solution would initiate a premature reaction. Thus, both active ingredients are subjected to spray drying with a so-called pneumatic nozzle from solution.

6. Spray-drying processes of solutions under conditions mentioned above result in extremely fine powders with particles of about 1 to 20 μm. 'Accordingly, claim 8 of the '44015 Application logically sets forth particles, wherein 90% are between 10 and 20 μm. Although claim 1 of the '44015 Application refers to soluble, free-flowing microparticles, the free-flowing nature of their product is doubtful due to the small particle size.

7. Figure 1, attached hereto, shows spray-dried microparticles prepared from a solution of bearberry leaf extract. The particle size is in the range of 1 to 10 μm. The hollow-sphere structure is clearly evident from the blow hole in the particle in the middle of the picture. The picture is characteristic for all spray-dried products prepared from solution using a pneumatic nozzle. Hollow microspheres in the range of 1 to 20 μm are always produced and form cohesive powders with a very low apparent density. These powders are difficult to handle, are cohesive and cause problems during further processing, transport and storage. A further disadvantage of the '44015 Application is that in spray drying from solution it is possible only to process the individual components (fibrinogen and thrombin) separately, and the spray-dried products must then be mixed. It is thus impossible from the outset to prepare a product containing both substances together.

8. By contrast, the '682 Application describes granules prepared in a fluidized bed. This entails, for example, an active ingredient concentrate being sprayed from aqueous solution onto a crystalline starting material consisting of a sugar or sugar alcohol. In addition, barrier layers can be applied. The resulting granules usually have a particle size of 30 to 500 μm, preferably 40 to 200 μm. They are thus free-flowing, can be spread, and are rapidly dissolving due to its hydrophilic nature.

9. In principle, the fluidized bed technology makes the following variations possible:

1. Preparation of thrombin-containing granules.
2. Preparation of fibrinogen-containing granules.

3. Preparation of a mixed product composed of the two granules from 1 and 2.

4. Preparation of fibrinogen granules which are subsequently provided with a barrier layer onto which thrombin can be applied in the outer layer. Polyvinylpyrrolidone and water-soluble cellulose derivatives or carbohydrates are suitable as a barrier layer.

5. Preparation of granules with one of the two active ingredients from aqueous solution and subsequent application of the second active ingredient suspended in an organic solvent. Use of an organic solvent in the second stage avoids premature coagulation between fibrinogen and thrombin.

10. The resulting fluidized bed granules are dust-free, with the particle sizes previously specified, free-flowing and easily metered. The morphology of these particles is depicted in Figure 2 for fibrinogen fluidized bed granules and in Figure 3 for thrombin fluidized bed granules. Both Figures are attached. The particles exhibit the typical slightly porous granule structure. They are not hollow spheres.

11. The spray-drying process described in the '44015 Application leads to microparticles with sizes in the range from 1 to 20 μm having hollow-sphere characteristics. They are easily crushed, cohesive and cause difficulties during further processing, transport and storage.

12. The granules described in the '682 Application are compact, slightly porous solid

particles not having hollow-sphere characteristics. The size range is preferably from 40 to 200 μm, resulting in a dust free product with improved flow properties. The granules have rapid dissolution characteristics.

13. Using spray drying, it is possible only to process thrombin and fibrinogen separately. The two active ingredients cannot be processed together in aqueous solution because of coagulation. The separate granules must subsequently be mixed in the desired ratio. By contrast, fluidized bed granulation makes it possible to prepare both separate granules of the two active ingredients and combination products. Possibilities in the preparation of combination products are both preparation without a barrier layer through the use of the second active ingredient in an organic suspension, and preparation with inclusion of a barrier layer and thus separation of the two active ingredients on the same core.

14. Spray drying from solution with pneumatic nozzles always results in microparticles having sizes in the range of 1 to 20 μm with a hollow-sphere structure. Such particles are usually not free-flowing and are cohesive. Granulation preferentially affords particles with sizes of the order of 40 to 200 μm, and coarser particle size distributions can also be achieved using appropriate process parameters. These coarse distributions have improved flow properties, reduced dust formation and rapid dissolution.

15. In summary, therefore, it must be stated that there are considerable differences between the two products, and the '682 Application represents a clear advance over the '44015

Application.

16. I declare further that statements made in this Declaration are of my own knowledge and are true and that all statements made on information and belief are believed to be true and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed on January 29, 2003

P. C. Schmidt

Prof. P. C. Schmidt

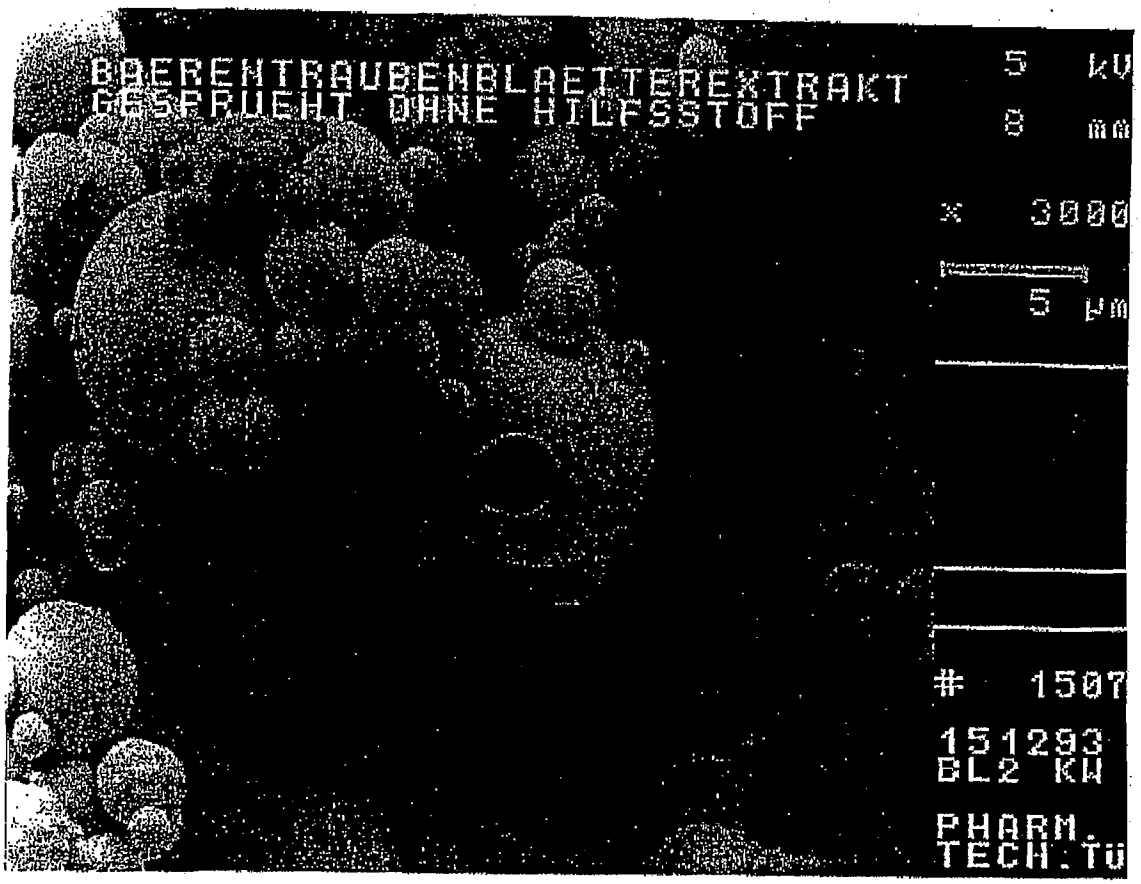

Figure 1: Spray-dried microparticles of barberry leaf extract (comparison product)

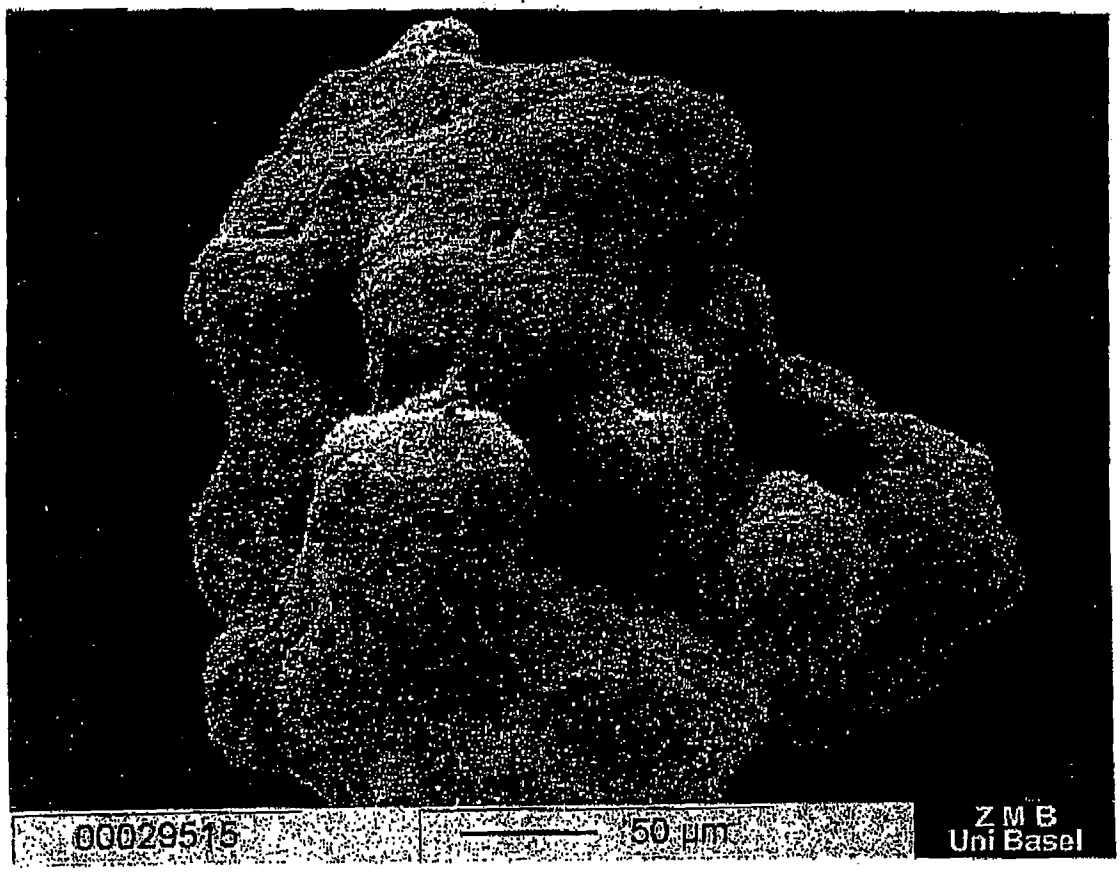

Figure 2: Fluidized bed fibrinogen granules

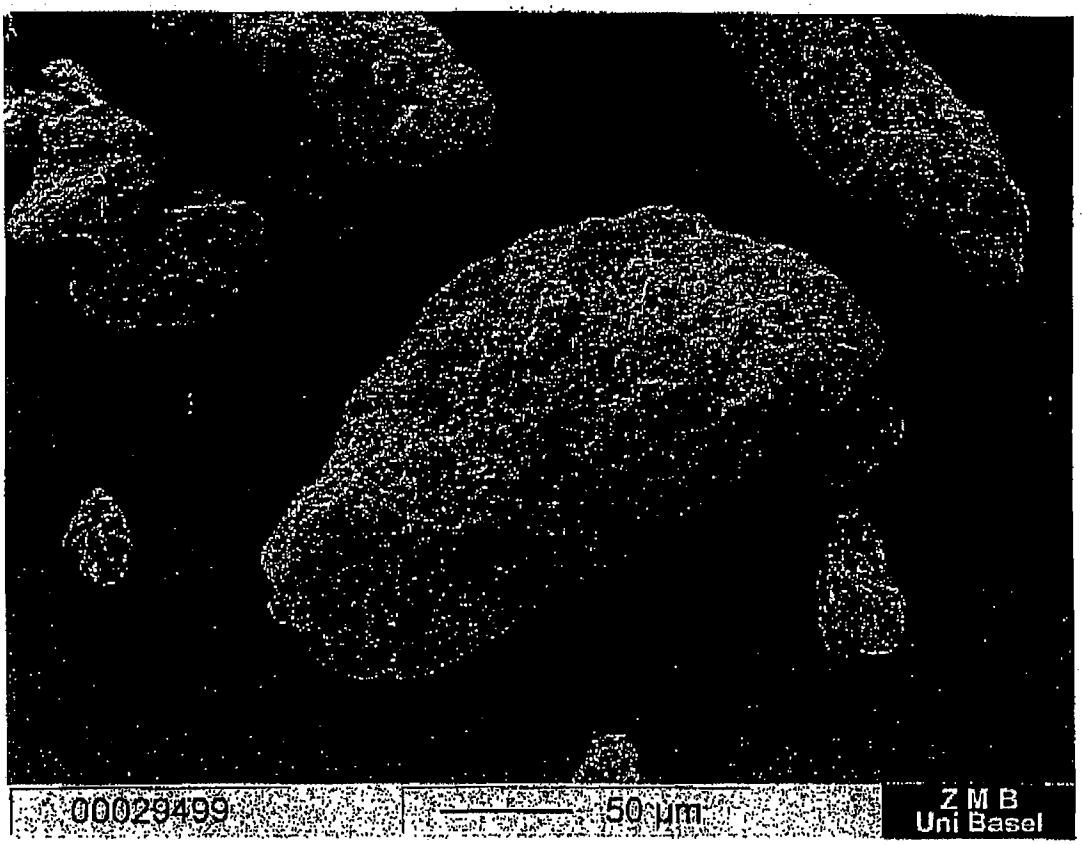

Figure 3: Fluidized bed thrombin granules

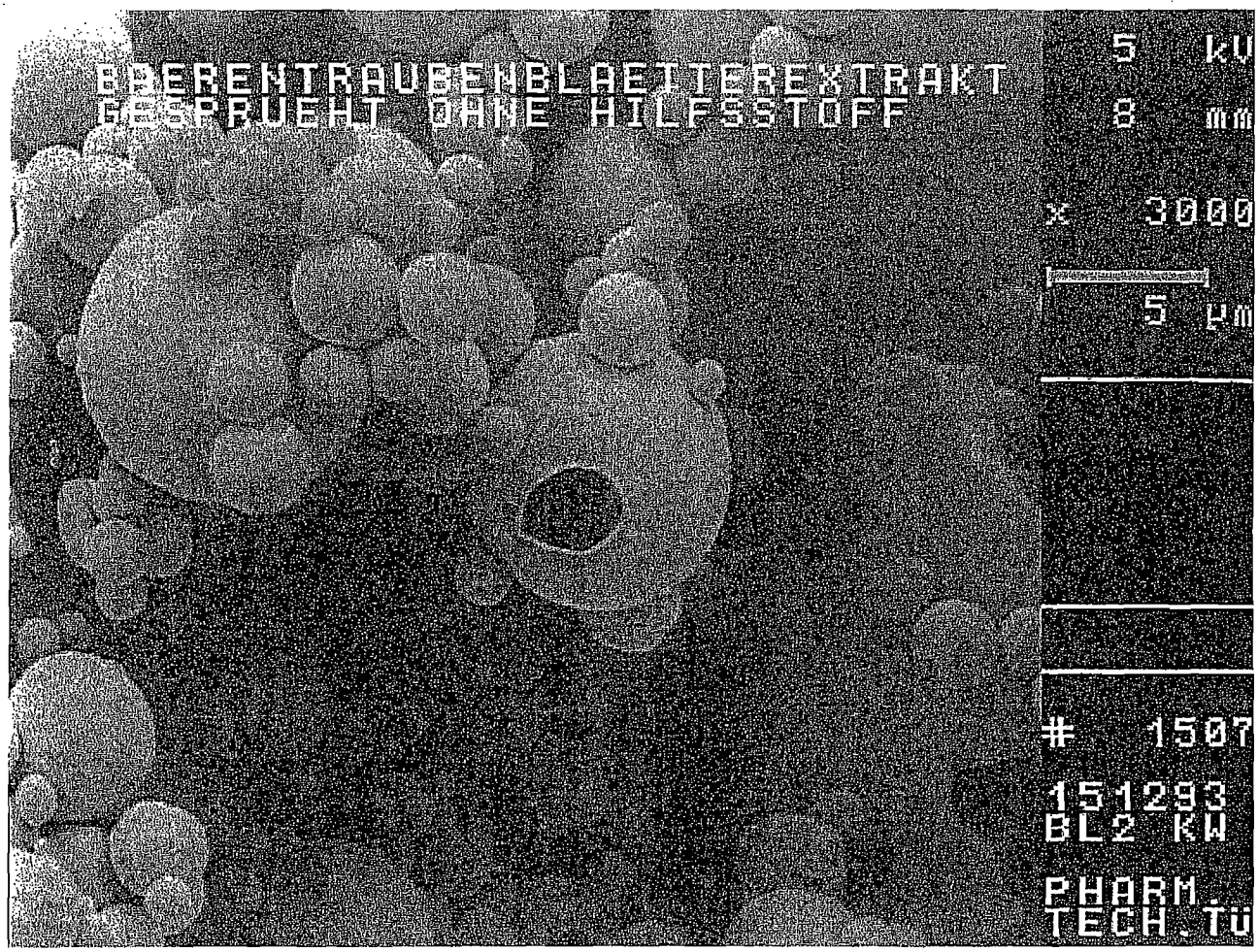

Abbildung 1: Sprühgetrocknete Mikropartikeln aus Bärentraubenblätter-Extrakt (Vergleichspräparat)

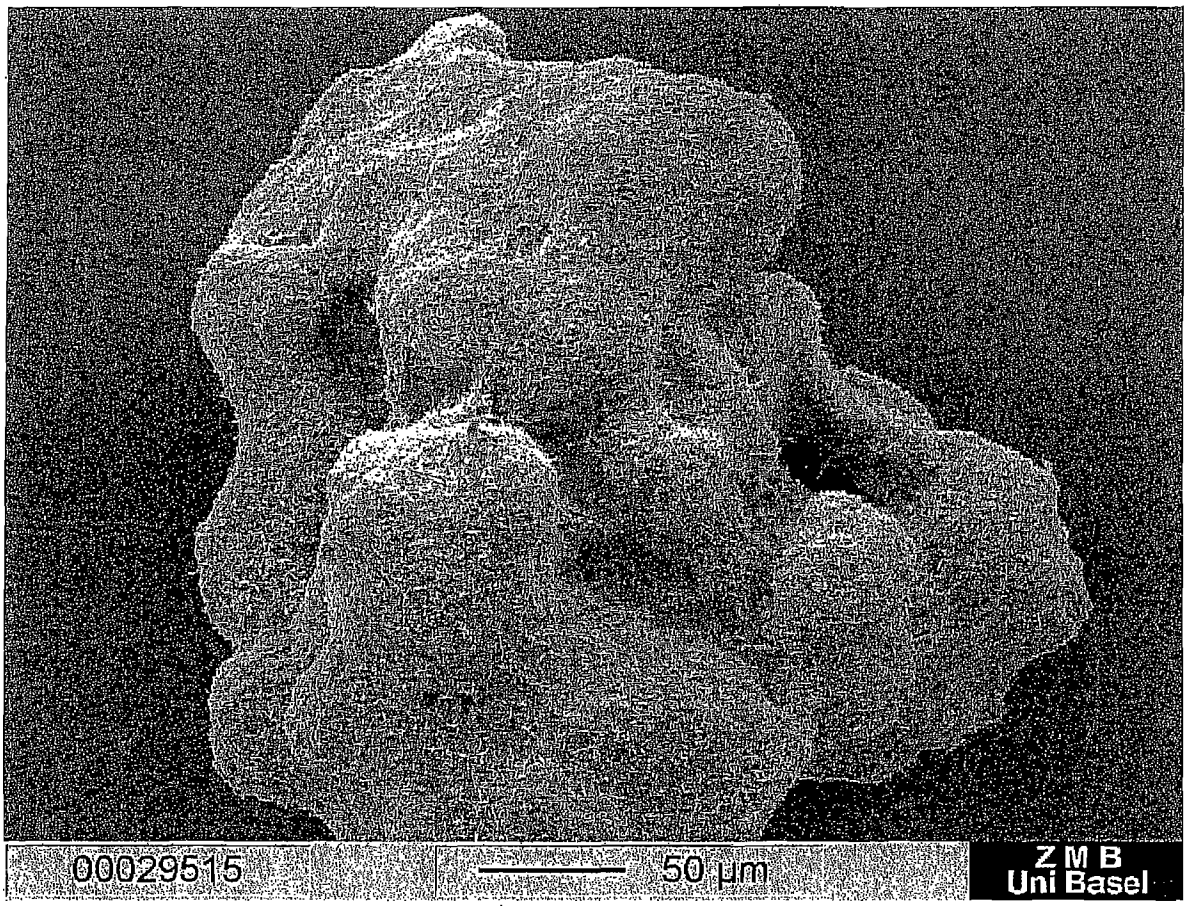

Abbildung 2: Wirbelschichtgranulat eines Fibrinogen-Granulates

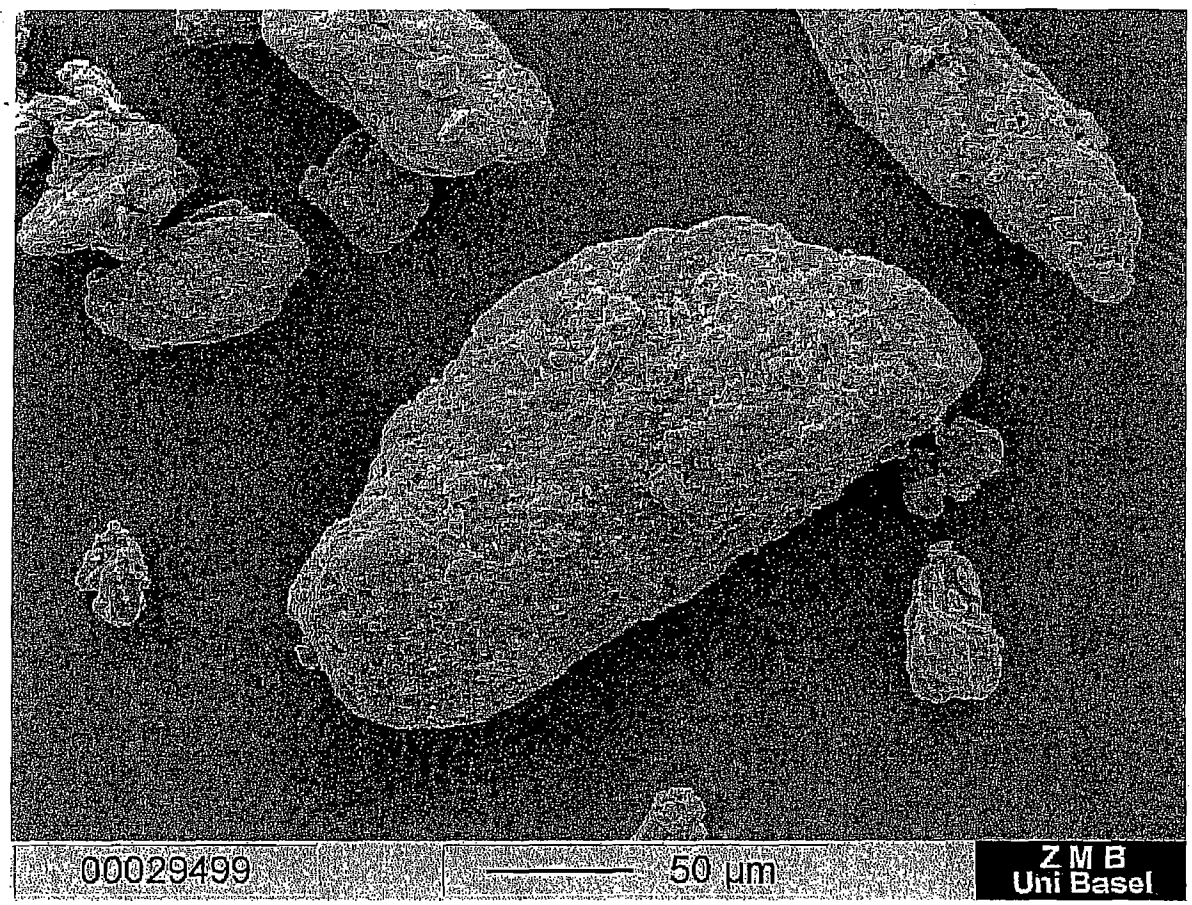

Abbildung 3: Wirbelschichtgranulat eines Thrombin-Granulates

Curriculum Vitae

Peter Christian Schmidt	born on March 4, 1940
1964 - 1967	Study of Pharmacy at the University of Erlangen/Nürnberg, Germany
1967 - 1970	University of Hamburg, Ph. D. Thesis: "The determination of micelle molecular weights of tensides by gel chromatography", supervisor: Prof. Dr. Heinz Sucker
1970 - 1981	Research and development in the pharmaceutical industry in Germany and Switzerland, main interests:development of solid dosage forms and medicaments from plants
1981 – 1988	Professor for Pharmaceutical Technology at the University of Marburg
1984 – 1985	Dean of the Faculty
1984 – 1988	Director of the Institute at the University of Marburg
since 1988	Professor for Pharmaceutical Technology at the University of Tuebingen, Germany
	Head of the Department for Pharmaceutical Technology
1991 - 1994	Director of the Institute for Pharmacy
1992 - 1994	Dean of the Faculty for Chemistry and Pharmacy
Research activities	Instrumentation of tablet machines, development of solid dosage forms and new tablet excipients, dry powder inhalations, film coating, development and stabilization of medicaments from plants, supercritical fluid extraction
Publications	around 190 papers, 20 patents and book chapters,
	two books: „Phytopharmaceutical Technology“ and „Wirk- und Hilfsstoffe für Rezeptur, Defektur und Großherstellung“
Other activities	Member of several associations like AAPS, German Pharmaceutical Association, International Association for Pharmaceutical Technology (APV), head of two working groups within the last two associations for several years. Member of the Scientific Committee of the German Advisory Board of Pharmacist, Adjunct professor at the University of Cincinnati, Visiting professor at he Universities of Addis Ababa, Ethiopia, Porto Alegre and Natal, Brazil, University of Lisbon, Portugal and University of Ljubljana, Slovenia
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Tuebingen, January 29, 2003

Publikationsliste Prof. Dr. P. C. Schmidt

1998 bis 2002

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